



Fondaparinux Versus Nadroparin for Prevention of Venous Thromboembolism After Elective Hip and Knee Arthroplasty[☆]



Mahmut Argun, MD, Mithat Oner, MD, Mehmet Saglamoglu, MD, Ibrahim Karaman, MD*, Ahmet Guney, MD, Mehmet Halici, MD, Ibrahim Halil Kafadar, MD

Department of Orthopaedics and Traumatology, Erciyes University Medical Faculty, Kayseri, Turkey

ARTICLE INFO

Article history:

Accepted 7 February 2013

Key Words:

arthroplasty
fondaparinux
nadroparin
venous thromboembolism

ABSTRACT

Objective: To evaluate the efficacy and safety of fondaparinux compared with nadroparin for prevention of venous thromboembolism after arthroplasty.

Patients and methods: One hundred fifteen patients were randomized into 2 treatment groups. Patients were given fondaparinux in Group I and nadroparin in Group II. Measurements were performed on Days 1, 5, and 21. The wound area was assessed with a subjective visual analog scale.

Results: The blood counts, clinical biochemical tests, and coagulation tests (ie, thrombin time, partial thromboplastin time, activated partial thromboplastin time, fibrinogen, prothrombin time–International Normalized Ratio, and antithrombin III activity) did not show statistically significant differences between Group I and Group II. In both study groups, anti-factor Xa activities increased significantly on the fifth and 21st day. The scores of the subjective visual analog scale showed significance on Day 21.

Conclusions: Our results confirm the safety and efficacy of both fondaparinux and nadroparin for prophylaxis after major orthopedic surgery.

© 2013. The Authors. Published by Elsevier Inc. All rights reserved.

Introduction

Venous thromboembolism (VTE), which presents clinically as deep vein thrombosis (DVT) and pulmonary embolism, is the most frequent serious complication after major orthopedic surgery of the lower extremities.^{1,2} At present, anticoagulant prophylactic treatments such as low-dose heparin, low-molecular-weight heparins (LMWHs), warfarin, or recombinant hirudin are recommended, but the frequency of venographically proven DVT still ranges from 16% to 30%.³

The development of LMWHs has added a new dimension to the clinical management of thrombotic disorders. LMWHs are prepared by the enzymatic or chemical depolymerization of standard heparin. The growing use of LMWH in the prophylaxis and treatment of acute thrombotic disorders emphasizes the need for characterization of the platelet effects of these anticoagulants.⁴

Fondaparinux (Arixtra; Organon Sanofi-Synthelabo LLC, Oss, the Netherlands) a pentasaccharide, is a selective inhibitor of coagulation factor Xa and interrupts the coagulation cascade by inhibiting thrombin generation without inactivating thrombin. This drug has been shown to be superior to LMWHs in the prevention of DVT after hip or knee replacement, and at least as effective and as safe as LMWHs and unfractionated heparin in patients with pulmonary embolism and DVT.^{5,6}

Nadroparin calcium (Fraxiparine; Sanofi, Winthrop, France) is an LMWH with a mean molecular weight of 4500 Daltons. Nadroparin calcium is a fractionated heparin derivative with a wide clinical spectrum of use as an anticoagulant for thromboprophylaxis to reduce the incidence of DVT.⁷

In our prospective, randomized study we aimed to assess the efficacy and safety of fondaparinux compared with nadroparin for prevention of VTE in patients undergoing elective hip and knee replacement surgery.

Patients and Methods

Patients

Patients of both sexes were eligible if they were aged 25 years or older and were scheduled for primary elective total hip and knee replacement surgery.

[☆]This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

* Address correspondence to: Ibrahim Karaman, MD, Department of Orthopaedics and Traumatology, Erciyes University Medical Faculty, TR-38039, Kayseri, Turkey.

E-mail address: drikaraman@gmail.com (I. Karaman).

We excluded patients if bilateral surgery was planned during the same procedure or within 2 weeks after inclusion. We also excluded patients who had at least 1 of the following criteria: major orthopedic surgery within the previous 1 month; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; history of haemorrhagic stroke or myocardial infarction within the previous 6 months; brain, spinal, or ophthalmologic surgery within the previous 3 months; history of malignancy, DVT, or pulmonary embolism; planned indwelling intrathecal or epidural catheter for more than 6 hours after the end of surgery; hypersensitivity to heparin, LMWHs, porcine products, or iodinated contrast media; uncontrolled hypertension (ie, diastolic blood pressure >120 mm Hg, systolic blood pressure >200 mm Hg); platelet count <100 × 10³/μL; hepatic and renal insufficiency; or anticoagulant treatment or any type of anti-coagulant or fibrinolytic therapy or dextran within the 2 days preceding the first administration of the study drug.

Study design

This open, prospective, comparative randomized study was carried out in a university hospital medical center over a period of 1 year. A total of 115 patients were randomized into 2 treatment groups.

In Group I, patients were assigned to once-daily subcutaneous injections of 2.5 mg fondaparinux 6 hours before surgery. The first injection of fondaparinux took place a mean of 12 hours after the operation and subsequent injections of 2.5 mg fondaparinux was given once daily.

In Group II, the first subcutaneous injection of nadroparin calcium was given 12 hours before surgery, the second 12 hours after completion of surgery, and subsequent injections once daily in the morning. The dose of the nadroparin was arranged in accordance with the manufacturer's recommendation.

The day of surgery was defined as Day 1 and the efficacy outcome was assessed on Day 5 and Day 21. During follow-up, patients were instructed to report any symptoms or signs of venous thromboembolism or bleeding, and any other clinical event that arose after treatment had been completed. If VTE arose during the study, treatment was left to the discretion of the investigator.

Intra- and postoperative bleeding was assessed, first according to the clinical impression of the surgeon (recorded as normal, greater than normal, or less than normal), and then by recording the blood loss collected by suction and swabs, drainage volume, and the number and amount of blood transfusions.

Throughout the treatment period, intermittent pneumatic compression, dextran, thrombolytic treatment, and any other anticoagulant agents were prohibited. The patients were advised to avoid taking aspirin or nonsteroidal anti-inflammatory drugs whenever possible. Use of graduated compression stockings and physiotherapy was recommended.

Measurements, including blood counts, clinical biochemical tests, and coagulation tests were done before the surgical procedure and on the fifth and 21st days after surgery. Blood counts included hemoglobin and hematocrit levels and platelet counts; clinical biochemical tests included alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, and direct and indirect bilirubin. Coagulation tests included thrombin time, partial thromboplastin time, activated partial thromboplastin time, fibrinogen, prothrombin time-International Normalized Ratio, antithrombin III activity, anti-factor Xa activity, and anti-IIa activity.

Bruising of the wound area was assessed by the same observer with use of a subjective visual analog scale described by Warwick

et al⁸ on the fifth and 21st postoperative days. With regard to bruising, a score of 0 points indicated no discoloration, 1 point indicated light-yellow discoloration, 2 points indicated dark-yellow discoloration, 3 points indicated yellow discoloration greater than the area of 3 palms, 4 points indicated yellow-and-black discoloration, and 5 points indicated yellow-and-black discoloration greater than the area of 3 palms.

The study was done in accordance with the ethical principles in the Declaration of Helsinki. The ethics committee of the university approved the protocol, and written informed consent was obtained from all patients before randomization.

Statistical Analysis

All statistical analysis was performed using SPSS 10.0 for Windows (IBM Corp, Armonk, New York). A *P* value of 0.05 or less was considered statistically significant. The outcomes were compared with use of the *t* test, the χ^2 test, the Mann-Whitney *U* test with a Bonferroni correction, and repeated measures analysis of variance test as appropriate.

Results

A total of 115 patients were randomized to receive either fondaparinux or nadroparin into 2 treatment groups over a period of 1 year.

Thirty-eight of 60 patients in Group I underwent total hip arthroplasty (THA), remaining 22 underwent total knee arthroplasty (TKA). Two THA and 3 TKA patients were excluded from the study due to the postoperative hematoma that was treated with drainage. Twenty-eight of 55 patients in Group II underwent THA, the remaining 27 underwent TKA. Two of the TKA patients were excluded from the study due to postoperative wound hematoma that was treated with drainage. There was not a significant difference between the groups in terms of hematoma frequency (*P* > 0.05). Serious adverse effects like thrombocytopenia, anemia, and allergy were not seen in either group. The remaining 55 (91.7%) patients in Group I and 53 (96.4%) patients in Group II completed the study (*P* > 0.05).

Baseline characteristics, including age, sex distribution of the patients, and the number of patients who had systemic disease like diabetes and hypertension were similar in both groups (see [Table I](#)) (*P* > 0.05).

The intraoperative blood loss, whether judged clinically or according to aspirated volume, and the mean volume of intraoperative blood transfusion did not show statistically significant differences in either group (*P* > 0.05).

When we evaluated the blood counts, including hemoglobin and hematocrit levels and platelet counts, we found that there was no statistically significant difference between groups.

Table I
Distribution of patients by age, sex, and systemic disease.*

	Group I	Group II	<i>P</i>
Age, y	58.7 (13.6)	60.0 (8.4)	> 0.05
Women	34 (61.8)	33 (62.2)	> 0.05
Men	21 (38.2)	20 (37.8)	> 0.05
Diabetes mellitus	5 (9.1)	4 (7.5)	> 0.05
Hypertension	12 (21.8)	10 (18.9)	> 0.05

* Except for age, which is presented as mean (SD), values are given as n (%).

Table II

The results of clinical biochemical tests of both groups on Day 1, 5, and 21.*

Test	Day 1	Day 5	Day 21	F	<i>P</i> [†]	<i>P</i> [‡]	<i>P</i> [§]	<i>P</i>
BUN, mg/dL								
Group I	16.7 (6.6)	17.8 (11.4)	17.1 (8.0)	6.7	0.07	0.26	0.09	0.29
Group II	14.8 (3.9)	14.2 (3.7)	14.9 (4.4)	1.08	0.35			
Creatinin, mg/dL								
Group I	0.78 (0.2)	0.9 (0.57)	0.95 (0.5)	1.5	0.24	0.30	0.30	0.10
Group II	0.74 (0.1)	0.78 (0.1)	0.7 (0.16)	2.4	0.10			
AST, U/l								
Group I	24.8 (6.0)	31.5 (12.4)	26.3 (9.4)	2.8	0.08	0.07	0.06	0.15
Group II	23.0 (4.9)	26.2 (7.1)	21.6 (6.1)	1.2	0.3			
ALT, U/l								
Group I	21.5 (14.3)	18.6 (9.4)	20.8 (8.8)	0.54	0.60	0.7	0.06	0.11
Group II	22.6 (6.2)	23.7 (10.0)	25.2 (6.9)	2.02	0.15			
Tbil, mg/dL								
Group I	0.76 (0.25)	0.78 (0.17)	0.86 (0.27)	1.4	0.26	0.23	0.97	0.09
Group II	0.72 (0.26)	0.75 (0.3)	0.71 (0.2)	5.7	0.11			
Ibil, mg/Dl								
Group I	0.19 (0.96)	0.21 (0.11)	0.24 (0.16)	6.0	0.05	0.58	0.62	0.06
Group II	0.20 (0.91)	0.23 (0.14)	0.21 (0.1)	6.2	0.07			

AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ibil, indirect bilirubin; Tbil, total bilirubin.

* Values for Days 1, 5, and 21 are given as mean (SD).

† Value for the comparison of a parameter in a group between the days.

‡ Value for the comparison of a parameter between groups on Day 1.

§ Value for the comparison of a parameter between groups on Day 5.

|| Value for the comparison of a parameter between groups on Day 21.

The results of clinical biochemical tests and coagulation tests are presented in **Table II** and the results of coagulation tests are shown in **Table III**.

Clinical biochemical tests, including alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, direct and indirect bilirubin, and coagulation tests, including thrombin time, partial thromboplastin time, activated partial thromboplastin time, fibrinogen, prothrombin time, prothrombin

time-International Normalized Ratio, and antithrombin III activity did not show statistically significant differences between Group I and Group II ($P > 0.05$). In both study groups, antifactor Xa activities increased significantly on the fifth and 21st day ($P < 0.05$). The antifactor Xa activity was higher in the fondaparinux group than the nadroparin group. Although the anti-IIa activity did not show significance between days ($P > 0.05$), it showed significance between groups on Day 1, Day 5, and Day 21

Table III

Results of coagulation tests of both groups on Day 1,5, and 21.*

Test	Day 1	Day 5	Day 21	F	<i>P</i> [†]	<i>P</i> [‡]	<i>P</i> [§]	<i>P</i>
TT, sec						0.06	0.90	0.88
Group I	12.5 (0.7)	12.3 (1.0)	12.6 (0.9)	2.2	0.13			
Group II	12.1 (0.4)	12.4 (0.6)	12.5 (0.7)	2.5	0.09			
PTZ, sec						0.40	0.45	0.70
Group I	11.9 (0.9)	12.2 (0.7)	12.4 (0.5)	5.1	0.16			
Group II	12.0 (0.8)	12.3 (1.2)	12.5 (0.7)	6.1	0.06			
aPTT, sec						0.27	0.36	0.11
Group I	28.7 (3.6)	29.5 (3.6)	29.4 (2.9)	0.6	0.56			
Group II	27.7 (1.7)	28.3 (2.9)	27.4 (4.7)	6.4	0.06			
PT-INR						0.56	0.18	0.14
Group I	0.94 (0.11)	0.95 (0.2)	0.96 (0.09)	4.0	0.23			
Group II	0.95 (0.08)	0.97 (0.1)	0.98 (0.1)	5.3	0.08			
Fibrinogen, mg/dL						0.60	0.08	0.95
Group I	407.0 (69.4)	606.0 (131.0)	592.0 (125.0)	36.0	0.07			
Group II	398 (94.6)	595.0 (152.0)	594.0 (197.0)	27.7	0.11			
AT-III, %						0.45	0.26	0.06
Group I	110.0 (10.4)	108.5 (12.6)	111.5 (12.5)	0.02	0.98			
Group II	112.7 (13.0)	113.7 (22.4)	109.0 (19.5)	7.5	0.09			
Anti-IIa, %						0.03	0.02	0.04
Group I	83.8 (26.2)	80.6 (17.5)	86.5 (23.2)	4.4	0.10			
Group II	98.2 (17.7)	103.6 (23.3)	101.8 (18.6)	4.3	0.13			
Anti-Xa, U/mL						0.13	0.35	0.99
Group I	0.03 (0.04)	0.2 (0.12)	0.19 (0.10)	34.1	0.01			
Group II	0.01 (0.006)	0.16 (0.12)	0.18 (0.13)	21.7	0.01			

Anti-FIIa, antifactor IIa; Anti-Xa, anticoagulation factor Xa; aPTT, activated partial thromboplastin time; AT III, antithrombin III; PT INR, prothrombin time-International Normalized Ratio; PTZ, partial thromboplastin time; TT, thrombin time.

* Values for Days 1, 5, and 21 are given as mean (SD).

† Value for the comparison of a parameter in a group between the days.

‡ Value for the comparison of a parameter between groups on Day 1.

§ Value for the comparison of a parameter between groups on Day 5.

|| Value for the comparison of a parameter between groups on Day 21.

Table IV
Visual analog scale scores.

Group	n	Day 5 (0-5)	Day 21 (0-5)	P*
Group I	55	2.63	2.61	0.58
Group II	53	2.76	1.43	0.01
P†		0.31	0.01	

* Value for the comparison of the score in a group between Days 5 and 21.
† Value for the comparison of the score between groups.

($P < 0.05$). Anti-IIa activity was significantly higher in nadro-
parin group ($P < 0.05$).

When we evaluated the scores of the subjective visual analog
scale, although there was not a statistically significant difference
between groups on the fifth day, we found significance on Day 21
(**Table IV**).

Only 1 proximal DVT occurred in a patient in Group II at the
19th day, which was confirmed by Doppler ultrasonography.
None of the patients in the study developed major bleeding
during the study period.

Discussion

VTE is a common, serious complication after major orthopedic
surgery of the lower extremities.^{1,2} Because of the high risk of VTE
and its considerable morbidity and mortality after major ortho-
pedic surgery of the lower extremities, the routine use of VTE
prophylaxis is recommended for all patients undergoing hip and
knee arthroplasty.²

Studies of the time course of VTE events after THA and TKA
have also demonstrated that when VTE prophylaxis is used, the
period over which patients are at risk is extended beyond 1 week,
and events are likely to occur after a patient is discharged from
the hospital.^{2,9} A retrospective study in a large group found that
76% of patients who had undergone THA and 47% who had
undergone TKA experienced a VTE event after being discharged
from the hospital.² Median time of diagnosis of thromboembo-
lism was 17 days with THA and 7 days with TKA. In our study, we
followed patients for 3 weeks, which included the period over
which patients are at high risk.

A meta-analysis of fondaparinux Phase III data in 5385
patients showed that, in patients who have had major orthopedic
surgery, fondaparinux reduced the incidence of VTE to 6.8% and
this result was better than the results of enoxaparin (13.7%).¹⁰

Nadroparin thromboprophylaxis is known to reduce the inci-
dence of DVT by 87%. This major decrease in DVT incidence was
not associated with an increased risk of bleeding.¹¹

In the Evaluation of AriXtra for the Prevention of vEnous
thRomboembolism in daily pracTice study¹² it was reported that
the overall rate of major bleeding with fondaparinux prophylaxis
was 0.8%, of which 71.4% of cases occurred within 15 days after
surgery. Fatal bleeding and bleeding in a critical organ was
observed in 0.1% of patients. Bleeding at the surgical site leading
to reoperation occurred in 0.5% of patients and bleeding at a
nonsurgical site necessitating the transfusion of >2 units of blood
occurred in 0.1% of patients. In our small study group, bleeding at
the surgical site leading to drainage due to postoperative hema-
toma occurred in 8.3% of patients in the fondaparinux group and
3.6% in the nadroparin group. Although the percentage was high
in the fondaparinux group there was not a statistically significant
difference between the 2 groups. None of the patients in the
2 groups had bleeding that was fatal or involved a critical organ.

In a Phase III, long-term prophylactic study in hip fracture
surgery, it was reported that there were no differences in the
overall incidence of adverse events and in platelet count between

the fondaparinux and placebo groups. However, until the safety of
fondaparinux concerning immune thrombocytopenia is firmly
established by clinical experience, periodic blood platelet count
monitoring is recommended during the course of fondaparinux
therapy.¹³ Similarly, an increase in serum transaminases was rare
in both groups.¹⁴

In our study, there were no differences between fondaparinux
and nadroparin groups in the blood counts, including hemoglobin
and platelet counts. When we evaluated the serum transami-
nases, although there was a slight increase in the mean value of
AST on the fifth and 21st day in both groups, the difference
showed no significance.

It is known that LMWH does not usually elevate activated
partial thromboplastin time; it is valued for its antithrombotic
rather than its anticoagulant effect.¹⁵ None of the coagulation
tests showed significant changes in either group of our study. In
general, antifactor Xa assays are more sensitive to the effects of
LMWHs and are therefore more useful in this respect than anti-IIa
assays.^{16,17} Differences were also observed in the antifactor Xa
activities of the LMWHs. All the LMWHs studied had weaker
antifactor Xa potency than standard heparin. We found that
antifactor Xa activities were increased significantly on the fifth
and 21st day in our both study groups.

Regarding the subjective visual analog scale, there was sig-
nificantly less bruising and oozing on the 21st day in the
nadroparin group than in the fondapainux group. The clinical
importance of these differences is unclear because it is not known
how they are related to the cost of the dressings, the duration of
hospitalization, the formation of hematomas, or the rate of
infection. Furthermore, the scales for the measurement of bruising
and oozing were subjective and the examination depends on
the observer. Unless these side effects were not to be associated
with the disastrous complication of infection, it would not be
viewed as a disadvantage.

In our prospective study, symptomatic VTE events were rare,
during both the treatment and follow-up periods. Our results
confirm the safety and efficacy of both fondaparinux and nadro-
parin for prophylaxis after major orthopedic surgery of the lower
extremities and showed that neither drug is associated with a risk
of major bleeding complications.

Acknowledgments

All authors contributed equally to the creation of the manuscript.

Conflicts of Interest

The authors have indicated that they have no conflicts of
interest regarding the content of this article.

References

- [1] Frostick SP. Death after joint replacement. *Haemostasis*. 2000;30:84–87.
- [2] White RH, Romano PS, Zhou H, et al. Incidence and time course of
thromboembolic outcomes following total hip or knee arthroplasty. *Arch
Intern Med*. 1998;158:1525–1531.
- [3] Nicolaides AN. Prevention of venous thromboembolism: international con-
sensus statement, guidelines compiled in accordance with the scientific
evidence. *Int Angiol*. 2001;20:1–37.
- [4] McMillan WD, McCarthy WJ, Lin SJ, et al. Perioperative low molecular weight
heparin for infrageniculate bypass. *J Vasc Surg*. 1997;25:796–802.
- [5] Turpie AG, Gallus AS, Hoek JA. Pentasaccharide Investigators. A synthetic
pentasaccharide for the prevention of deep-vein thrombosis after total hip
replacement. *N Engl J Med*. 2001;344:619–625.
- [6] Bauer KA, Hawkins DW, Peters PC, et al. Fondaparinux, a synthetic penta-
saccharide: the first in a new class of antithrombotic agents—the selective
factor Xa inhibitors. *Cardiovasc Drug Rev*. 2002;20:37–45.

- [7] Yoo MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *Intl Orthop*. 1997;21:399–402.
- [8] Warwick D, Jeffrey H, David G, et al. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement: a prospective, randomized trial. *J Bone Joint Surg*. 1998;80:1158–1165.
- [9] Sikorski JM, Hampson WG, Staddon GE. The natural history and aetiology of deep vein thrombosis after total hip replacement. *J Bone Joint Surg Br*. 1981;63-B:171–177.
- [10] Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162:1833–1840.
- [11] Pareint GD, Wessinger SJ, Harris WH. Survey of prophylaxis against venous thromboembolism in adults undergoing hip surgery. *Clin Orthop*. 1987;232:188–193.
- [12] Singelyn FJ, CPMC Verheyen, Piovella F, et al. The safety and efficacy of extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limb with or without a neuraxial or deep peripheral nerve catheter: The EXPERT Study. *Anesth Analg*. 2007;105:1540–1547.
- [13] Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. No episode of thrombocytopenia after four-week administration of fondaparinux, a new synthetic and selective inhibitor of factor Xa, in the PENTHIFRAPLUS study. *J Thromb Haemos*. 2003;1:2050.
- [14] Lassen MR, Eriksson BI. Absence of transaminase increase after four-week administration of fondaparinux (Arixtraw), a new synthetic and selective inhibitor of factor Xa, in the PENTHIFRA-PLUS study. *J Thromb Haemos*. 2003;1:2052.
- [15] Lensing AW, Prins MH, Davidson BL, Hirsch J. Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis. *Arch Intern Med*. 1995;155:601–607.
- [16] Samama M. Contemporary laboratory monitoring of low molecular weight heparins. *Thromb Haemost*. 1995;15:119–123.
- [17] Fareed J, Jeske W, Hoppensteadt D, Clarizio R, Walenga JM. Low-molecular-weight heparins: pharmacologic profile and product differentiation. *Am J Cardiol*. 1998;82:3–10.